Association between serum uric acid, aortic, carotid and femoral stiffness among adults aged 40-75 years without and with type 2 diabetes mellitus: The Maastricht Study

Original Article

Association between serum uric acid, aortic, carotid and femoral stiffness among adults aged 40–75 years without and with type 2 diabetes mellitus: The Maastricht Study

José M.A. Wijnands[a,b], Annelies Boonen[a,b], Thomas T. van Sloten[c,d,e], Miranda T. Schram[c,d], Simone J.S. Sep[c,d], Annemarie Koster[b,f], Carla J.H. van der Kallen[c,d], Ronald M.A. Henry[c,d] Pieter C. Dagnelie[b,d,g], Coen D.A. Stehouwer[c,d], Sjef van der Linden[a,b], and Ilja C.W. Arts[b,d,g]

See editorial comment on page 1531

Objective: Arterial stiffness may be a mechanism to explain the association between uric acid and cardiovascular disease. We aimed to analyse associations between serum uric acid and regional and local arterial stiffness, and assess potential differences related to sex and glucose metabolism status.

Methods: A cross-sectional study was performed in 614 adults [52.6% men; mean age 58.7 ± 8.5 years; 23.2% type 2 diabetes mellitus (by design)] from The Maastricht Study. Arterial stiffness was assessed by carotid–femoral pulse wave velocity (cfPWV), distensibility, and compliance coefficient of the carotid and femoral artery, and carotid artery Young's elastic modulus.

Results: Higher uric acid (per SD of 74 μmol/l) was associated with greater stiffness indicated by a significantly higher cfPWV [$\beta = 0.216$ (95% confidence interval 0.061, 0.372); $P = 0.006$] and lower carotid distensibility coefficient [$\beta = -0.633$ (95% confidence interval −1.099, −0.166); $P = 0.008$] after adjustment for sex, age, and glucose metabolism status. Associations lost significance after adjusting for mean arterial pressure, BMI, waist, smoking status, heart rate, total : high-density lipoprotein cholesterol ratio, triglycerides, estimated glomerular filtration rate, use of lipid-lowering, antihypertensive, and diabetes medication, and use of secondary uricosurics. No associations were found between uric acid and carotid compliance coefficient, carotid Young's elastic modulus, or stiffness of the femoral artery. A significant interaction ($P < 0.10$) with glucose metabolism status was found for cfPWV. However, none of the stratified associations were significant. There was no interaction with sex.

Conclusion: Uric acid was not significantly associated with stiffness of the aorta, or the carotid or femoral artery among adults aged 40–75 years without and with type 2 diabetes mellitus.

Keywords: compliance coefficient, distensibility coefficient, pulse wave velocity, uric acid, Young's elastic modulus

Abbreviations: Δ*D*, distension; baPWV, brachial–ankle pulse wave velocity; cfPWV, carotid–femoral pulse wave velocity; cIMT, carotid intima–media thickness; *D*, arterial diameter; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; YEM, Young's elastic modulus

INTRODUCTION

The prevalence of hyperuricaemia in the general population has been estimated at 10–20% [1–4]. There is accumulating evidence that hyperuricaemia is associated with cardiovascular disease (CVD) and its risk factors [5]. The exact mechanisms underlying this association, however, are not completely understood. Arterial stiffness could be a mechanism that links uric acid to CVD.

Arterial stiffness is the loss of elastic properties of the arterial wall and can contribute to CVD through the development of systolic hypertension, left ventricular hypertrophy, and impaired coronary perfusion [6]. Stiffness is affected by endothelial cell function and vascular smooth muscle cell tone [7]. Both underlying processes have been reported to be modified by uric acid [8–10]. Arterial stiffness can be measured at different arterial segments and sites, and by use of different techniques which include regional carotid–femoral pulse wave velocity (cfPWV), brachial–ankle PWV (baPWV), and local carotid and femoral stiffness. Several studies have assessed the association between

Journal of Hypertension 2015, 33:1642–1650

[a]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Centre, [b]CAPHRI School for Public Health and Primary Care, Maastricht University, [c]Department of Internal Medicine, Maastricht University Medical Centre, [d]CARIM School for Cardiovascular Diseases, [e]NUTRIM School for Nutrition, Toxicology and Metabolism, [f]Department of Social Medicine and [g]Department of Epidemiology, Maastricht University, Maastricht, the Netherlands

Correspondence to José M.A. Wijnands, MSc, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands. Tel: +31 43 3875026; fax: +31 43 3875006; e-mail: wijnandsjose@gmail.com

Received 22 April 2014 **Revised** 5 March 2015 **Accepted** 5 March 2015

DOI:10.1097/HJH.0000000000000593

uric acid and regional arterial stiffness, with conflicting results [11–21]. However, in most of these studies [12,14,16–20], arterial stiffness was determined via the assessment of baPWV. cfPWV is a more established index of arterial stiffness and is considered the 'gold standard' [6]. cfPWV involves a mixture of elastic and muscular arterial parts of the arterial tree, and is independently associated with CVD [22,23]. Studies examining the association between uric acid and cfPWV, however, have also shown inconsistent results [11,15,21,24–28], possibly due to incomplete adjustment for confounding factors such as glucose metabolism status [11,24], renal function [11], mean arterial pressure [26], or antihypertensive medication [25], and a large variation in study populations.

Studies that investigated the relation between uric acid and local arterial stiffness indices are scarce [29,30]. However, assessing local carotid stiffness indices may be of importance [6]. The carotid artery is a frequent site of atheroma formation [6], and combined with greater carotid stiffness, the risk of ischemic stroke may increase [31]. This could be explained by the association between increased pulse pressure (PP) and plaque instability [32]. In addition, stiffening of peripheral arteries, such as the femoral artery, may also be important in the development of CVD, because stiffness of these arteries may boost the premature return of reflected pulse waves [33].

Previous longitudinal studies have reported a stronger relation between uric acid and CVD or mortality in women than in men [34,35]. In addition, research suggests a difference in the association between uric acid and CVD according to glucose metabolism status [36], possibly due to a biological interaction between uric acid, glucose, and insulin concentrations [37,38]. In view of these considerations, we investigated whether uric acid is associated with cfPWV, local carotid and/or femoral stiffness. In addition, interactions between uric acid, sex, and glucose metabolism status were assessed.

METHODS

Study population and design

In this study, we used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously [39]. In brief, the study focuses on the aetiology, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus (T2DM) and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status for reasons of efficiency. The present report includes cross-sectional data from the first 866 participants, who completed the baseline survey between November 2010 and March 2012. The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Netherlands Health Council under the Dutch 'Law for Population Studies' (Permit 131088–105234-PG). All participants gave written informed consent.

For the present study, we excluded patients without data on uric acid ($N=13$), cfPWV ($N=43$), local carotid stiffness ($N=54$), local femoral stiffness ($N=86$), smoking status ($N=17$), BMI ($N=1$), waist ($N=3$), cholesterol concentrations ($N=8$), and/or estimated glomerular filtration rate (eGFR) ($N=9$). We also excluded individuals with type 1 diabetes ($N=4$) or a history of CVD ($N=152$). A history of CVD was defined as self-reported myocardial infarction; cerebrovascular infarction or haemorrhage; and/or percutaneous artery angioplasty or vascular surgery of the coronary, abdominal, peripheral, or carotid arteries according to the Rose questionnaire [40]. Furthermore, individuals taking any uric acid-lowering medication (i.e. allopurinol or benzbromaron; $N=21$) were excluded. The total study population thus consisted of 614 participants.

Arterial stiffness measurements

All measurements were done by trained vascular technicians, unaware of the participants' clinical or diabetes status, in a dark, quiet, temperature-controlled room (21–23°C). Participants were asked to refrain from smoking and drinking coffee, tea, or alcoholic beverages 3 h prior to the study. Participants were allowed to have a light meal (breakfast and/or lunch). All measurements were performed in the supine position after 10 min of rest. Talking or sleeping was not allowed during the examination. During the vascular measurements (approximately 45 min), brachial systolic, diastolic, and mean arterial pressure (MAP) were determined every 5 min with an oscillometric device (Accutorr Plus, Datascope Inc., Montvale, New Jersey, USA). The mean MAP and heart rate (HR) of these measurements were used in the statistical analysis. A three-lead electrocardiogram was recorded continuously during the measurements to facilitate automatic signal processing.

Carotid–femoral pulse wave velocity

Carotid–femoral PWV was determined according to recent guidelines [41], with the use of applanation tonometry (SphygmoCor, Atcor Medical, Sydney, Australia). Pressure waveforms were determined at the right common carotid and right common femoral arteries. The difference in the time of pulse arrival from the R-wave of the electrocardiogram between the two sites (transit time) was determined with the intersecting tangents algorithm. The pulse wave travel distance was calculated as 80% of the direct straight distance (measured with an infantometer) between the two arterial sites. The median of three consecutive cfPWV (defined as travelled distance/transit time) recordings was used in the analyses.

Local arterial stiffness

Measurements were done at the left common carotid (10 mm proximal to the carotid bulb) and the right common femoral (10–20 mm proximal to the flow divider) arteries, with the use of an ultrasound scanner equipped with a 7.5-MHz linear probe (MyLab 70, Esaote Europe B.V., Maastricht, the Netherlands). This set-up enables the measurement of diameter, distension, and intima-media

thickness (IMT) as described previously [42,43]. Briefly, during the ultrasound measurements, a B-mode image on the basis of 19 M-lines was depicted on screen. An online echo-tracking algorithm showed real-time anterior and posterior wall displacements. The M-mode recordings were composed of 19 simultaneous recordings at a frame rate of 498 Hz. The distance between the M-line recording positions was 0.96 mm; thus, a total segment of 18.24 mm of each artery was covered by the scan plane. For offline processing, the radiofrequency signal was fed into a dedicated computer-based acquisition system (ART.LAB, Esaote Europe B.V. Maastricht, the Netherlands) with a sampling frequency of 50 MHz. Data processing was performed in MatLab (version 7.5; Mathworks, Natick, Massachusetts, USA). The distension waveforms were obtained from the radiofrequency data with the use of a wall track algorithm [42]. Carotid IMT was defined as the distance of the posterior wall from the leading edge interface between lumen and intima to the leading edge interface between media and adventitia [43]. The median diameter, distension and IMT of the three measurements were used in the analyses.

Data analysis was done by quantifying the local arterial elastic properties through the calculation of the following indices [44]:

1. Distensibility coefficient $= (2\Delta D \times D + \Delta D^2)/(\mathrm{PP} \times D^2)$ $(10^{-3}/\mathrm{kPa})$
2. Young's elastic modulus (YEM) (carotid artery only) $= D/(\mathrm{IMT} \times \text{distensibility coefficient})$ $(10^3\,\mathrm{kPa})$
3. Compliance coefficient $= \pi \times (2D \times \Delta D + \Delta D^2)/4\mathrm{PP}$ $(\mathrm{mm}^2/\mathrm{kPa})$

where D is the arterial diameter; ΔD is the distension; IMT the intima–media thickness; and PP the pulse pressure (i.e. brachial and carotid PP for calculating femoral and carotid stiffness indices, respectively). Brachial PP was calculated as SBP minus DBP. Carotid PP was calculated according to the calibration method described by Kelly and Fitchett [45], with the use of carotid tonometry wave forms as adapted by van Bortel *et al.* [46]. This method assumes a constant difference between MAP and diastolic pressure along the arterial tree. PP can then be calculated at a carotid artery (PPcar) from the uncalibrated carotid pressure waveform using the formula: $\mathrm{PPcar} = \mathrm{PPcar}_{\mathrm{uncalibrated}} \times (\mathrm{Kbrach}/\mathrm{Kcar}_{\mathrm{uncalibrated}})$, in which K is defined as (MAP − diastolic pressure). For the carotid artery, diastolic pressure and MAP are calculated as the minimum and the area under the tonometry waveform divided by time, respectively.

Distensibility coefficient represents arterial stiffness; YEM, the stiffness of the arterial wall material at operating pressure; and compliance coefficient, the arterial buffering capacity. Note that higher values of cfPWV or carotid YEM, and lower values of distensibility coefficient or compliance coefficient denote greater arterial stiffness, that is, lower arterial elasticity.

Reproducibility was assessed by two observers in 12 individuals (6 men, 60.8 ± 6.8 years; 6 individuals with T2DM) who were examined on two occasions spaced 1 week apart. The intra-observer and inter-observer intra-class correlation coefficients were 0.87 and 0.69 for cfPWV; 0.85 and 0.73 for carotid distensibility coefficient; 0.95 and 0.72 for carotid compliance coefficient; 0.72 and 0.71 for carotid YEM; 0.49 and 0.32 for femoral distensibility coefficient; and 0.41 and 0.67 for femoral compliance coefficient.

Other covariates

After an overnight fast, venous blood samples were collected at The Maastricht Study research centre. Plasma glucose was measured with a standard enzymatic hexokinase reference method, and serum total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, creatinine, and uric acid concentrations were measured with standard (enzymatic and/or colourimetric) methods by an automatic analyser (Beckman Synchron LX20; Beckman Coulter Inc., Brea, USA) at Maastricht University Medical Centre (the Netherlands). Measurement of creatinine was based on the Jaffé method traceable to isotope dilution mass spectrometry (Synchron LX20; Beckman Coulter Inc.). Height (in centimetres) was measured with individuals standing upright against a stadiometer. Body weight was measured on an analogue scale (Seca 761; Seca, Hamburg, Germany). BMI was calculated as body weight (kg) divided by height squared (m^2). Waist circumference was measured in duplicate midway between the lower rib margin and the iliac crest at the end of expiration, to the nearest 0.5 cm, with a flexible plastic tape measure (Seca). Participants were requested to bring all the medication they used at the time of measurement or a list from their pharmacists to the research centre. During a medication interview generic name, dose and frequency, and additional over-the-counter (OTC) medication use were registered by trained staff. All participants received an extensive web-based questionnaire in which smoking behaviour (never, former, current) and years of diabetes duration was self-reported. SBP and DBP was determined three times on the right arm after a 10-min resting period, using a blood pressure monitor (Omron 705 IT; Omron, Japan). The average of the three measurements was calculated. Hypertension was defined as office SBP above 140 mmHg, or DBP above 90 mmHg, and/or current antihypertensive medication use. Renal function as estimated by GFR (in ml/min per 1.73 m^2) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [47]. To determine glucose metabolism, all participants (except those who used insulin) underwent a standardized 2-h-75-g oral glucose tolerance test (OGTT) after an overnight fast. For safety reasons, participants with a fasting glucose level above 11.0 mmol/l ($N = 13$) were excluded from the OGTT. Glucose metabolism status was classified according to the WHO 2006 criteria [48] as: normal glucose metabolism (NGM) in case of fasting plasma glucose concentrations below 6.1 mmol/l and 2-h post-glucose concentrations below 7.8 mmol/l; impaired glucose tolerance (IGT) in case of fasting plasma glucose below 7.0 mmol/l and 2-h post-glucose at least 7.8 mmol/l and less than 11.1mmol/l; impaired fasting glucose (IFG) in case of fasting plasma glucose 6.1–6.9 mmol/l and (if measured) 2-h post-glucose below 7.8 mmol/l; and T2DM in case of fasting plasma glucose at least 7.0 mmol/l and/or 2-h

post-glucose at least 11.1 mmol/l. For this study, we defined having either IFG or IGT as impaired glucose metabolism (IGM).

Statistical analysis

All analyses were performed using IBM SPSS version 19.0 (SPSS, Chicago, Illinois, USA). General characteristics of the study population were compared across tertiles of uric acid concentrations using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. Multivariable linear regression analyses were used to determine the association between uric acid [per +1 standard deviation (SD), SD = 74 μmol/l] and arterial stiffness indices (cfPWV, carotid distensibility coefficient, carotid compliance coefficient, carotid YEM, femoral distensibility coefficient, and femoral compliance coefficient). The associations were first adjusted for age, sex, and glucose metabolism status (model 1). Additionally, the associations were adjusted for BMI, waist, smoking status, HR (for analyses with cfPWV only), total : HDL cholesterol ratio, triglycerides, eGFR, use of lipid-lowering and diabetes medication, renin–angiotensin–aldosterone system inhibitors, and other antihypertensive medication (including beta-blockers) that have no known uricosuric properties, and antihypertensive and lipid-lowering medication that may have a uricosuric effect, that is, secondary uricosurics [including losartan (N = 14) [49,50], amlodipine (N = 18) [51], atorvastatin (N = 39) [52], and rosuvastatin (N = 36)] [52] (model 2). None of the individuals used fenofibrate [53].

Arteries become stiffer when they are distended [54] and therefore stiffness is highly dependent on blood pressure. Elastin fibres bear the load at physiologic pressures, while collagen fibres remain folded [55]. However, with increasing pressures, stiffer collagen fibres are recruited causing an increase in stiffness. In order to disentangle the effects of blood pressure from differences in stiffness properties of the arterial wall *per se*, we additionally adjusted for MAP in models 1 and 2. Interactions between uric acid and sex or glucose metabolism status were tested in model 2 + MAP using F change. Additionally, over-adjustment by eGFR as a potential intermediate variable in the association between uric acid and arterial stiffness indices was evaluated by excluding eGFR from model 2 + MAP [56,57].

A P value less than 0.05 was considered statistically significant, except for the interaction analyses, where P value less than 0.10 was used.

RESULTS

Table 1 shows the general characteristics of the study population according to uric acid tertiles. Of the total population of 614 individuals, 323 (52.6%) were men. The average age was 58.7 years. A large percentage of individuals had T2DM (23.2%) or hypertension (50.5%). Individuals in the third uric acid tertile were significantly older, more frequently male, and more often had T2DM and hypertension. Individuals excluded because of missing data had slightly higher uric acid concentrations, had a higher BMI, and more often had T2DM, hypertension, and a kidney function below 60 ml/min per 1.73 m^2 (Supplementary Table 1, http://links.lww.com/HJH/A482).

Uric acid and regional arterial stiffness

Linear regression analysis, adjusted for age, sex, and glucose metabolism status, showed that a 1 SD (74 μmol/l) higher serum uric acid concentration was associated with a higher cfPWV [β = 0.216; 95% confidence interval (CI) 0.061, 0.372; P = 0.006] (Table 2, model 1). After adjustment for MAP, the association became non-significant (β = 0.108; 95% CI —0.031, 0.247; P = 0.127). Additional adjustment for BMI, waist, smoking status, HR, total : HDL cholesterol ratio, triglycerides, eGFR, use of lipid-lowering, diabetes, and antihypertensive medication, and secondary uricosurics, did not materially change the results (β = 0.110; 95% CI −0.055, 0.275; P = 0.190) (Table 2, model 2 + MAP). Results of model 2 with or without adjustment for MAP were similar (β = 0.134; 95% CI −0.048, 0.317; P = 0.149) (Table 2, model 2). No interaction between uric acid and sex (P for interaction = 0.589) was identified in the association between uric acid and cfPWV. Glucose metabolism status modified the association (P for interaction = 0.096). However, after full adjustment (model 2 + MAP), uric acid was not significantly associated with cfPWV in any of the subgroups of individuals with normal glucose metabolism (N = 369) (β = −0.127; 95% CI −0.329, 0.076; P = 0.219), IGM (N = 102) (β = 0.206; 95% CI −0.188, 0.601; P = 0.301), or with T2DM (N = 143) (β = 0.338; 95% CI −0.075, 0.752; P = 0.108).

Uric acid and local arterial stiffness

After adjustment for age, sex, and glucose metabolism status, higher uric acid was associated with greater stiffness indicated by a significantly lower carotid distensibility coefficient (β = −0.663; 95% CI −1.099, −0.166; P = 0.008) (Table 3, model 1). Uric acid was not associated with carotid compliance coefficient, carotid YEM, femoral distensibility coefficient, or femoral compliance coefficient (Table 3, model 1). The significant association with carotid distensibility coefficient was lost after adjustment for MAP (β = −0.268; 95% CI −0.672, 0.136; P = 0.193) (Table 3, model 1 + MAP). Additional adjustment for the confounding factors in model 2 did not materially change the result (β = −0.196; 95% CI −0.679, 0.288; P = 0.427) (Table 3, model 2 + MAP). Results of model 2 with or without adjustment for MAP were similar (β = −0.287; 95% CI −0.845, 0.271; P = 0.313) (Table 3, model 2).

No significant interactions between uric acid, sex, and glucose metabolism status were identified in the associations between uric acid and any of the local stiffness indices (data not shown – all P values for interaction >0.110).

Additional analyses

After excluding eGFR from the list of confounders in model 2 + MAP, the association between uric acid and cfPWV became stronger (β = 0.171; 95% CI 0.012, 0.329; P = 0.035). Excluding eGFR from the analyses did not change the results of the associations between uric acid and the local stiffness indices (data not shown).

TABLE 1. Baseline characteristics of The Maastricht Study population according to tertiles of uric acid

	Overall ($N=614$)	Uric acid tertiles			*P* value[a]
		Lowest ($N=196$)	Middle ($N=216$)	Highest ($N=202$)	
Uric acid (μmol/l)	346 ± 74	267 ± 29	339 ± 20	431 ± 47	<0.001
Age (years)	58.7 ± 8.5	57.4 ± 8.1	58.6 ± 8.7	60.1 ± 8.5	0.007
Male sex (%)	52.6	24.0	58.3	74.3	<0.001
BMI (kg/m^2)	26.8 ± 4.3	25.0 ± 3.7	26.7 ± 3.8	28.8 ± 4.5	<0.001
Waist circumference (cm)	95.5 ± 12.8	88.9 ± 11.9	94.9 ± 11.5	102.5 ± 11.4	<0.001
Smoking (%)					0.321
Never	33.1	35.2	31.5	33.7	
Past	51.5	46.9	51.9	55.4	
Current	15.5	17.9	16.7	11.9	
Total cholesterol-to-HDL ratio	4.2 ± 1.3	3.7 ± 1.1	4.3 ± 1.3	4.7 ± 1.4	<0.001
Triglycerides (mmol/l)	1.18 (0.83; 1.74)	0.92 (0.67; 1.34)	1.26 (0.84; 1.69)	1.48 (1.05; 2.24)	<0.001
Use of lipid-lowering medication[b] (%)	15.3	8.2	18.5	18.8	0.003
eGFR (ml/min per 1.73 m^2)	85.9 ± 14.2	89.2 ± 12.2	87.3 ± 13.5	81.4 ± 15.4	<0.001
eGFR <60 ml/min per 1.73 m^2 (%)	4.7	1.0	3.2	9.9	<0.001
Glucose metabolism status (%)					<0.001
Normal glucose metabolism	60.1	76.0	60.2	44.6	
Impaired glucose metabolism	16.6	8.7	17.1	23.8	
Type 2 diabetes	23.2	15.3	22.7	31.7	
Diabetes treatment among individuals with type 2 diabetes[c] (%)					0.002
No medication	23.1	26.7	24.5	20.3	
Oral medication[d]	60.8	46.7	61.2	67.2	
Insulin with or without oral medication	16.1	26.6	14.3	12.5	
Diabetes duration[c] (years)	7.0 (3.0; 11.0)	7.0 (3.3; 11.8)	6.0 (3.0; 11.0)	7.0 (2.0; 10.0)	0.767
Hypertension (%)	50.5	31.1	53.7	65.8	<0.001
Use of antihypertensive medication among individuals with hypertension[b,e] (%)					
Use of RAAS inhibitors	39.7	37.7	31.9	47.4	0.042
Use of other antihypertensive medication	38.7	26.2	34.5	48.1	0.007
Use of secondary uricosurics (%)	15.8	13.8	16.2	17.3	0.611
Mean arterial pressure (mmHg)	97.4 ± 10.1	94.5 ± 10.7	98.4 ± 9.9	99.2 ± 9.2	<0.001
Brachial pulse pressure (mmHg)	51.1 ± 9.8	48.6 ± 9.4	51.7 ± 9.9	52.9 ± 9.5	<0.001
Carotid pulse pressure[f] (mmHg)	49.9 ± 13.6	46.9 ± 12.7	50.4 ± 14.0	52.2 ± 13.7	<0.001
Heart rate (b.p.m.)	68.2 ± 10.4	68.5 ± 10.0	67.4 ± 10.3	68.8 ± 10.8	0.390
Carotid–femoral pulse wave velocity (m/s)	8.7 ± 2.0	8.2 ± 1.7	8.8 ± 1.9	9.2 ± 2.3	<0.001
Carotid artery[g]					
Distensibility coefficient (10^{-3}/kPa)	15.3 ± 6.3	16.2 ± 6.9	15.3 ± 6.1	14.4 ± 5.8	0.015
Compliance coefficient (mm^2/kPa)	0.69 ± 0.30	0.68 ± 0.30	0.70 ± 0.29	0.68 ± 0.30	0.687
Young's elastic modulus (10^3 kPa)	0.72 ± 0.39	0.68 ± 0.44	0.70 ± 0.36	0.76 ± 0.35	0.093
Femoral artery[h]					
Distensibility coefficient (10^{-3}/kPa)	14.4 ± 8.2	14.9 ± 7.4	14.1 ± 8.4	14.2 ± 8.7	0.625
Compliance coefficient (mm^2/kPa)	1.06 ± 0.63	1.01 ± 0.52	1.07 ± 0.67	1.09 ± 0.69	0.393

ANOVA, analysis of variance; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; RAAS, renin–angiotensin–aldosterone system. Data are reported as mean ± SD, median (inter-quartile range), or percentage as appropriate.
[a]On the basis of ANOVA for continuous variables and chi-square tests for categorical variables.
[b]Not including medication that have known uricosuric properties.
[c]Individuals with type 2 diabetes: overall ($N=143$); lowest tertile ($N=30$); middle tertile ($N=49$); highest tertile ($N=64$).
[d]Including use of GLP-1 agonist ($N=2$).
[e]Individuals with hypertension: overall ($N=310$); lowest tertile ($N=61$); middle tertile ($N=116$); highest tertile ($N=133$).
[f]Carotid pulse pressure ($N=613$).
[g]Carotid distensibility and compliance coefficient ($N=601$), Young's elastic modulus ($N=600$).
[h]Femoral distensibility and compliance coefficient ($N=574$).

DISCUSSION

Accumulating evidence suggests that uric acid is associated with CVD [5]. Arterial stiffness, as one of the precursors of CVD, could therefore be among the underlying mechanisms. However, we found no evidence that uric acid was significantly associated with cfPWV or local carotid and femoral arterial stiffness indices in this population-based cohort study (including 23.2% with T2DM) of adults aged 40–75 years.

Non-significant associations between uric acid and cfPWV were also found in previous cross-sectional studies among normotensive ($N=656$) [25], untreated hypertensive ($N=647$ and $N=292$) [25,27], or hypertensive ($N=366$) individuals [24]. Similarly, no association was found by Lim *et al.* [26] in a healthy population free of CVD, diabetes, renal disease, hypertension, or dyslipidaemia ($N=1276$). In contrast, Liang *et al.* [15] did find a positive association between uric acid and cfPWV in a comparable, but larger, population ($N=3772$). Independent associations were also found in never-treated hypertensive individuals ($N=1225$) [21] and among workers ($N=940$) [11]. The heterogeneity in terms of sample size, population characteristics, and the adjustments made for confounding factors such as glucose

TABLE 2. The association between uric acid and regional stiffness

	cfPWV (m/s)[b]		
	β[a]	95% CI	*P* value
Model 1	0.216	0.061, 0.372	0.006
Model 1 + MAP	0.108	−0.031, 0.247	0.127
Model 2	0.134	−0.048, 0.317	0.149
Model 2 + MAP	0.110	−0.055, 0.275	0.190

Model 1: adjusted for sex, age, and glucose metabolism status. Model 2: model 1 + adjusted for heart rate, BMI, waist, smoking, total : HDL cholesterol, triglycerides, eGFR, use of lipid-lowering, diabetes, and antihypertensive medication, and use of secondary uricosurics. cfPWV, carotid–femoral pulse wave velocity; CI, confidence interval; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MAP, mean arterial pressure.
[a]Uric acid expressed per standard deviation (74 μmol/l).
[b]$N = 614$.

metabolism status or kidney function, between these studies, is large. We found no clear reason to explain the discrepancies in results.

Femoral and carotid arteries differ with regard to structure and function [58]. The muscular femoral artery has more vascular smooth muscle cells and a higher collagen-to-elastin ratio, and stiffening of this artery is less influenced by age and blood pressure than stiffening of the carotid artery [58]. In the present study, we found no difference in the associations between uric acid and femoral stiffness or carotid stiffness. In line with our study, Cipolli *et al.* [29] did not identify an association between uric acid and carotid YEM or carotid compliance coefficient in 338 individuals with hypertension. In addition, an association between uric acid and carotid distensibility coefficient was not found among young adults [30]. Our study is the first to evaluate the association between uric acid and the femoral artery and to compare the potential effect of uric acid on both carotid and femoral vessels.

In our models, we distinguished between effects of blood pressure on arterial stiffness and differences in stiffness properties of the arterial wall per se. After adding MAP to model 1 the β-coefficients decreased substantially. This suggests that the associations between uric acid, cfPWV, and carotid distensibility coefficient in model 1 were attributable to MAP. However, after adjusting model 1 for the confounding factors in model 2, additional adjustment for MAP did not influence our results. MAP is correlated with the confounding factors in model 2, such as kidney function and BMI. Since the independent effects of these factors cannot be disentangled, we cannot draw firm conclusions on the role of MAP in the association between uric acid and arterial stiffness.

A previous study found that a 1 SD increase in age (SD = 8.5 years), MAP (SD = 9.6 mmHg), or triglyceride concentrations (SD = 64.1 mg/dl) was significantly associated with an increase in cfPWV of 1.04, 0.59, and 0.24 m/s, respectively [59]. In our study, a 1 SD (74 μmol/l) increase in uric acid concentration was non-significantly ($P = 0.190$) associated with a 0.110 m/s higher cfPWV. Therefore, the magnitude of the association found in our study implies a very small, if any, contribution of uric acid to the development of aortic stiffness.

Excluding kidney function from the list of confounders in the additional analyses resulted in a stronger association between uric acid and cfPWV. This may be explained by the association between kidney function and arterial stiffness [56], and/or the association between kidney function and uric acid [57]. We cannot conclude whether kidney function acts as a confounder and/or as a mediator.

In our study, we did not find significant sex-related interactions in the associations between uric acid and any of the arterial stiffness indices. This is in line with other studies that investigated the association between uric acid and cfPWV in the general population [15] or in individuals with newly diagnosed hypertension [21]. In contrast, Chen *et al.* [11] identified a stronger relation between uric acid and arterial stiffness among men. An increase of 100 μmol/l serum uric acid was significantly associated with an increase of 0.15 m/s in cfPWV among men, whereas there was no association among women. The authors suggested that the null finding among women may be attributable to the small percentage of women with hyperuricaemia [11]. Although sex differences in the impact of elevated serum uric acid concentrations on CVD have often been observed, explanations for these differences are still lacking.

It has been suggested that uric acid may have a different effect on cardiovascular mortality according to glucose

TABLE 3. The association between uric acid and local stiffness of the carotid and femoral artery

		DC (10^{-3}/kPa)			CC (mm^2/kPa)			YEM (10^3 kPa)[b]		
		β[a]	95% CI	*P* value	β[a]	95% CI	*P* value	β[a]	95% CI	*P* value
Carotid artery[c]										
	Model 1	−0.633	−1.099, —0.166	0.008	−0.020	−0.044, 0.003	0.091	0.020	−0.012, 0.052	0.220
	Model 1 + MAP	−0.268	−0.672, 0.136	0.193	−0.007	−0.029, 0.015	0.522	0.002	−0.028, 0.032	0.902
	Model 2	−0.287	−0.845, 0.271	0.313	−0.016	−0.044, 0.013	0.277	0.006	−0.033, 0.045	0.752
	Model 2 + MAP	−0.196	−0.679, 0.288	0.427	−0.012	−0.039, 0.014	0.361	0.002	−0.035, 0.038	0.930
Femoral artery[d]										
	Model 1	−0.522	−1.283, 0.239	0.179	−0.027	−0.084, 0.029	0.343			
	Model 1 + MAP	−0.197	−0.937, 0.542	0.600	−0.006	−0.062, 0.050	0.832			
	Model 2	0.019	−0.903, 0.940	0.968	0.003	−0.065, 0.072	0.920			
	Model 2 + MAP	0.139	−0.755, 1.032	0.761	0.011	−0.055, 0.078	0.739			

Model 1: adjusted for sex, age, glucose metabolism status. Model 2: model 1 + adjusted for BMI, waist, smoking, total : HDL cholesterol, triglycerides, eGFR, use of lipid-lowering, diabetes, and antihypertensive medication and use of secondary uricosurics. CC, compliance coefficient; CI, confidence interval; DC, distensibility coefficient; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; MAP, mean arterial pressure; YEM, Young's elastic modules.
[a]Uric acid expressed per standard deviation (74 μmol/l).
[b]$N = 606$.
[c]$N = 608$.
[d]$N = 585$.

metabolism status [36], because of the possible biological interaction between uric acid, glucose, and insulin concentrations [37,38]. The Maastricht Study cohort was designed to find potential contrasts between individuals with and without T2DM. In the present study, we found a significant interaction between uric acid and glucose metabolism status in the association with cfPWV. The stratified results may suggest that the detrimental effect of uric acid is more apparent among individuals with IGM or T2DM as compared to those with normal glucose metabolism. However, we want to stress that none of the stratified associations was significant and the β-coefficients of the associations were relatively small. Furthermore, the subgroups according to glucose metabolism status differed in size. We therefore emphasize the need for replication of our findings on the glucose metabolism-related differences.

A limitation of this study is the exclusion of a proportion (∼5–10%) of individuals from the analyses because of missing values on one of the arterial stiffness indices. However, we assumed these missing values to be missing at random because most values were missing due to logistic factors such as the unavailability of a vascular ultrasound technologist. A further limitation is that the cross-sectional design does not allow conclusions on cause-and-effect relations.

The study was strengthened by the comprehensive evaluation of arterial stiffness, using both regional as well as local arterial stiffness indices. Moreover, vascular echography data were collected by trained vascular ultrasound technologists and benefited from the high repeatability of the aortic and carotid stiffness measurements. Additionally, due to the extensive phenotyping, we were able to adjust for a series of potential confounders.

In conclusion, we found no significant association between uric acid and aortic, carotid, or femoral stiffness among 614 adults aged 40–75 years without and with T2DM.

ACKNOWLEDGEMENTS

Source of funding: This study is supported by the European Regional Development Fund as part of OP-ZUID, the province of Limburg, the department of Economic Affairs of the Netherlands (grant 31O.041), Stichting the Weijerhorst, the Pearl String Initiative Diabetes, the Cardiovascular Centre Maastricht, CARIM School for Cardiovascular Diseases, NUTRIM School for Nutrition, Toxicology and Metabolism, Stichting Annadal, Health Foundation Limburg and by unrestricted grants from Janssen, Novo Nordisk and Sanofi.

Conflicts of interest

A.B. receives research grants for the department from Pfizer, AbbVie, Merck, Amgen and occasionally speakers' honoraria from Pfizer and UCB. For the remaining authors no conflicts of interest were declared.

REFERENCES

1. Uaratanawong S, Suraamornkul S, Angkeaw S, Uaratanawong R. Prevalence of hyperuricemia in Bangkok population. *Clin Rheumatol* 2011; 30:887–893.
2. Lohsoonthorn V, Dhanamun B, Williams MA. Prevalence of hyperuricemia and its relationship with metabolic syndrome in Thai adults receiving annual health exams. *Arch Med Res* 2006; 37:883–889.
3. Conen D, Wietlisbach V, Bovet P, Shamlaye C, Riesen W, Paccaud F, Burnier M. Prevalence of hyperuricemia and relation of serum uric acid with cardiovascular risk factors in a developing country. *BMC Public Health* 2004; 4:9.
4. Zhu Y, Pandya BJ, Choi HK. Comorbidities of gout and hyperuricemia in the US general population: NHANES 2007–2008. *Am J Med* 2012; 125:679–687.
5. Kanbay M, Segal M, Afsar B, Kang DH, Rodriguez-Iturbe B, Johnson RJ. The role of uric acid in the pathogenesis of human cardiovascular disease. *Heart* 2013; 99:759–766.
6. Laurent S, Cockcroft J, Van Bortel L, Boutouyrie P, Giannattasio C, Hayoz D, *et al*. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J* 2006; 27:2588–2605.
7. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol* 2005; 25:932–943.
8. Corry DB, Eslami P, Yamamoto K, Nyby MD, Makino H, Tuck ML. Uric acid stimulates vascular smooth muscle cell proliferation and oxidative stress via the vascular renin-angiotensin system. *J Hypertens* 2008; 26:269–275.
9. Kang DH, Han L, Ouyang X, Kahn AM, Kanellis J, Li P, *et al*. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol* 2005; 25:425–433.
10. Yu MA, Sanchez-Lozada LG, Johnson RJ, Kang DH. Oxidative stress with an activation of the renin-angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. *J Hypertens* 2010; 28:1234–1242.
11. Chen X, Li Y, Sheng CS, Huang QF, Zheng Y, Wang JG. Association of serum uric acid with aortic stiffness and pressure in a Chinese workplace setting. *Am J Hypertens* 2010; 23:387–392.
12. Ishizaka N, Ishizaka Y, Toda E, Hashimoto H, Nagai R, Yamakado M. Higher serum uric acid is associated with increased arterial stiffness in Japanese individuals. *Atherosclerosis* 2007; 192:131–137.
13. Khan F, George J, Wong K, McSwiggan S, Struthers AD, Belch JJ. The association between serum urate levels and arterial stiffness/endothelial function in stroke survivors. *Atherosclerosis* 2008; 200:374–379.
14. Kuo CF, Yu KH, Luo SF, Ko YS, Wen MS, Lin YS, *et al*. Role of uric acid in the link between arterial stiffness and cardiac hypertrophy: a cross-sectional study. *Rheumatology (Oxford)* 2010; 49:1189–1196.
15. Liang J, Li Y, Zhou N, Teng F, Zhao J, Zou C, Qi L. Synergistic effects of serum uric acid and cardiometabolic risk factors on early stage atherosclerosis: the cardiometabolic risk in Chinese study. *PLoS One* 2012; 7:e51101.
16. Park JS, Kang S, Ahn CW, Cha BS, Kim KR, Lee HC. Relationships between serum uric acid, adiponectin and arterial stiffness in postmenopausal women. *Maturitas* 2012; 73:344–348.
17. Saijo Y, Utsugi M, Yoshioka E, Horikawa N, Sato T, Gong YY, Kishi R. Relationships of C-reactive protein, uric acid, and glomerular filtration rate to arterial stiffness in Japanese subjects. *J Hum Hypertens* 2005; 19:907–913.
18. Shin JY, Lee HR, Shim JY. Significance of high-normal serum uric acid level as a risk factor for arterial stiffness in healthy Korean men. *Vasc Med* 2012; 17:37–43.
19. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T, *et al*. Influences of age and gender on results of noninvasive brachial-ankle pulse wave velocity measurement: a survey of 12517 subjects. *Atherosclerosis* 2003; 166:303–309.
20. Tsai WC, Huang YY, Lin CC, Li WT, Lee CH, Chen JY, Chen JH. Uric acid is an independent predictor of arterial stiffness in hypertensive patients. *Heart Vessels* 2009; 24:371–375.
21. Vlachopoulos C, Xaplanteris P, Vyssoulis G, Bratsas A, Baou K, Tzamou V, *et al*. Association of serum uric acid level with aortic stiffness and arterial wave reflections in newly diagnosed, never-treated hypertension. *Am J Hypertens* 2011; 24:33–39.
22. Maldonado J, Pereira T, Polonia J, Silva JA, Morais J, Marques M. Arterial stiffness predicts cardiovascular outcome in a low-to-moderate cardiovascular risk population: the EDIVA (Estudo de DIstensibilidade VAscular) project. *J Hypertens* 2011; 29:669–675.
23. Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as

index of arterial stiffness in the general population. *Circulation* 2006; 113:664–670.
24. Gomez-Marcos MA, Recio-Rodriguez JI, Patino-Alonso MC, Agudo-Conde C, Rodriguez-Sanchez E, Gomez-Sanchez L, *et al.* Relationship between uric acid and vascular structure and function in hypertensive patients and sex-related differences. *Am J Hypertens* 2013; 26:599–607.
25. Hsu PF, Chuang SY, Cheng HM, Sung SH, Ting CT, Lakatta EG, *et al.* Associations of serum uric acid levels with arterial wave reflections and central systolic blood pressure. *Int J Cardiol* 2013; 168:2057–2063.
26. Lim JH, Kim YK, Kim YS, Na SH, Rhee MY, Lee MM. Relationship between serum uric acid levels, metabolic syndrome, and arterial stiffness in korean. *Korean Circ J* 2010; 40:314–320.
27. Tsioufis C, Kyvelou S, Dimitriadis K, Syrseloudis D, Sideris S, Skiadas I, *et al.* The diverse associations of uric acid with low-grade inflammation, adiponectin and arterial stiffness in never-treated hypertensives. *J Hum Hypertens* 2011; 25:554–559.
28. Cicero AF, Salvi P, D'Addato S, Rosticci M, Borghi C. Association between serum uric acid, hypertension, vascular stiffness and subclinical atherosclerosis: data from the Brisighella Heart Study. *J Hypertens* 2014; 32:57–64.
29. Cipolli JA, Ferreira-Sae MC, Martins RP, Pio-Magalhaes JA, Bellinazzi VR, Matos-Souza JR, Junior WN. Relationship between serum uric acid and internal carotid resistive index in hypertensive women: a cross-sectional study. *BMC Cardiovasc Disord* 2012; 12:52.
30. Oikonen M, Wendelin-Saarenhovi M, Lyytikainen LP, Siitonen N, Loo BM, Jula A, *et al.* Associations between serum uric acid and markers of subclinical atherosclerosis in young adults. The cardiovascular risk in Young Finns study. *Atherosclerosis* 2012; 223:497–503.
31. Dijk JM, van der Graaf Y, Grobbee DE, Bots ML. Carotid stiffness indicates risk of ischemic stroke and TIA in patients with internal carotid artery stenosis: the SMART study. *Stroke* 2004; 35:2258–2262.
32. Lovett JK, Howard SC, Rothwell PM. Pulse pressure is independently associated with carotid plaque ulceration. *J Hypertens* 2003; 21:1669–1676.
33. van de Laar RJ, Ferreira I, van Mechelen W, Prins MH, Twisk JW, Stehouwer CD. Habitual physical activity and peripheral arterial compliance in young adults: the Amsterdam growth and health longitudinal study. *Am J Hypertens* 2011; 24:200–208.
34. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality the NHANES I epidemiologic follow-up study, 1971-1992. National Health and Nutrition Examination Survey. *J Am Med Assoc* 2000; 283:2404–2410.
35. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. *Ann Intern Med* 1999; 131:7–13.
36. Kramer CK, von Muhlen D, Jassal SK, Barrett-Connor E. A prospective study of uric acid by glucose tolerance status and survival: the Rancho Bernardo Study. *J Intern Med* 2010; 267:561–566.
37. Padova J, Patchefsky A, Onesti G, Faludi G, Bendersky G. The effect of glucose loads on renal uric acid excretion in diabetic patients. *Metabolism* 1964; 13:507–512.
38. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E. Effect of insulin on uric acid excretion in humans. *Am J Physiol* 1995; 268:E1–5.
39. Schram MT, Sep SJS, Kallen van der CJ, Dagnelie PC, Koster A, Schaper N, *et al.* The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epid* 2014; 29:439–451.
40. Leng GC, Fowkes FG. The Edinburgh Claudication Questionnaire: an improved version of the WHO/Rose Questionnaire for use in epidemiological surveys. *J Clin Epidemiol* 1992; 45:1101–1109.
41. Van Bortel LM, Laurent S, Boutouyrie P, Chowienczyk P, Cruickshank JK, De Backer T, *et al.* Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens* 2012; 30:445–448.
42. Hermeling E, Reesink KD, Kornmann LM, Reneman RS, Hoeks AP. The dicrotic notch as alternative time-reference point to measure local pulse wave velocity in the carotid artery by means of ultrasonography. *J Hypertens* 2009; 27:2028–2035.
43. Willekes C, Hoeks AP, Bots ML, Brands PJ, Willigers JM, Reneman RS. Evaluation of off-line automated intima-media thickness detection of the common carotid artery based on M-line signal processing. *Ultrasound Med Biol* 1999; 25:57–64.
44. Reneman RS, Meinders JM, Hoeks AP. Noninvasive ultrasound in arterial wall dynamics in humans: what have we learned and what remains to be solved. *Eur Heart J* 2005; 26:960–966.
45. Kelly R, Fitchett D. Noninvasive determination of aortic input impedance and external left ventricular power output: a validation and repeatability study of a new technique. *J Am Coll Cardiol* 1992; 20:952–963.
46. Van Bortel LM, Balkestein EJ, van der Heijden-Spek JJ, Vanmolkot FH, Staessen JA, Kragten JA, *et al.* Noninvasive assessment of local arterial pulse pressure: comparison of applanation tonometry and echo-tracking. *J Hypertens* 2001; 19:1037–1044.
47. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150:604–612.
48. WHO. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia: report of a WHO/IDF consultation*. Geneva, Switzerland: World Health Organization (WHO); 2006.
49. Takahashi S, Moriwaki Y, Yamamoto T, Tsutsumi Z, Ka T, Fukuchi M. Effects of combination treatment using antihyperuricaemic agents with fenofibrate and/or losartan on uric acid metabolism. *Ann Rheum Dis* 2003; 62:572–575.
50. Hamada T, Ichida K, Hosoyamada M, Mizuta E, Yanagihara K, Sonoyama K, *et al.* Uricosuric action of losartan via the inhibition of urate transporter 1 (URAT 1) in hypertensive patients. *Am J Hypertens* 2008; 21:1157–1162.
51. Chanard J, Toupance O, Lavaud S, Hurault de Ligny B, Bernaud C, Moulin B. Amlodipine reduces cyclosporin-induced hyperuricaemia in hypertensive renal transplant recipients. *Nephrol Dial Transplant* 2003; 18:2147–2153.
52. Ogata N, Fujimori S, Oka Y, Kaneko K. Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleos Nucleot Nucl* 2010; 29:321–324.
53. Uetake D, Ohno I, Ichida K, Yamaguchi Y, Saikawa H, Endou H, Hosoya T. Effect of fenofibrate on uric acid metabolism and urate transporter 1. *Intern Med* 2010; 49:89–94.
54. Greenwald SE. Ageing of the conduit arteries. *J Pathol* 2007; 211:157–172.
55. Roach MR, Burton AC. The reason for the shape of the distensibility curves of arteries. *Can J Biochem Physiol* 1957; 35:681–690.
56. Safar ME, London GM, Plante GE. Arterial stiffness and kidney function. *Hypertension* 2004; 43:163–168.
57. Sedaghat S, Hoorn EJ, van Rooij FJ, Hofman A, Franco OH, Witteman JC, Dehghan A. Serum uric Acid and chronic kidney disease: the role of hypertension. *PLoS One* 2013; 8:e76827.
58. Benetos A, Laurent S, Hoeks AP, Boutouyrie PH, Safar ME. Arterial alterations with aging and high blood pressure. A noninvasive study of carotid and femoral arteries. *Arterioscler Thromb* 1993; 13:90–97.
59. Mitchell GF, Parise H, Benjamin EJ, Larson MG, Keyes MJ, Vita JA, *et al.* Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: the Framingham Heart Study. *Hypertension* 2004; 43:1239–1245.

Reviewers' Summary Evaluations

Reviewer 1

The study adds fuel to the heated debate on the role of uric acid in arterial stiffness. Contradictory data have been published so far on the matter. The novelty of the study is the simultaneous assessment both of regional and local arterial stiffness. Limitations of the study include the small size of the cohort, which is limited to ages 40–75, where patients with type 2 diabetes mellitus are over-represented.

Reviewer 2

The aim of the study was to analyze associations between circulating uric acid and indices of arterial stiffness in a

general population. The authors' conclusion is that higher uric acid is associated with greater arterial stiffness, as indicated by significantly higher carotid-femoral pulse wave velocity; however this association is no more significant after adjustment for confounding factors.

The issue explored and the results obtained are interesting, suggesting that the observed association between uric acid and cardiovascular disease is not a direct one, but it is mediated by other risk factors. However, different results were obtained in at least another study.